Characterization of free breathing patterns with 5D lung motion model

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Purpose: To determine the quiet respiration breathing motion model parameters for lung cancer and nonlung cancer patients.

Methods: 49 free breathing patient 4DCT image datasets (25 scans, cine mode) were collected with simultaneous quantitative spirometry. A cross-correlation registration technique was employed to track the lung tissue motion between scans. The registration results were applied to a lung motion model: $\vec{X} = \vec{X}_0 + \vec{\alpha}v + \vec{\beta}f$, where $\vec{X}$ is the position of a piece of tissue located at reference position $\vec{X}_0$ during a reference breathing phase (zero tidal volume v , zero airflow f). $\vec{\alpha}$ is a parameter that characterizes the motion due to air filling (motion as a function of tidal volume v) and $\vec{\beta}$ is the parameter that accounts for the motion due to the imbalance of dynamical stress distributions during inspiration and exhalation that causes lung motion hysteresis (motion as a function of airflow f). The parameters $\vec{\alpha}$ and $\vec{\beta}$ together provide a quantitative characterization of breathing motion that inherently includes the complex hysteresis interplay. The $\vec{\alpha}$ and $\vec{\beta}$ distributions were examined for each patient to determine overall general patterns and interpatient pattern variations.

Results: For 44 patients, the greatest values of $|\vec{\alpha}|$ were observed in the inferior and posterior lungs. For the rest of the patients, $|\vec{\alpha}|$ reached its maximum in the anterior lung in three patients and the lateral lung in two patients. The hysteresis motion $\vec{\beta}$ had greater variability, but for the majority of patients, $|\vec{\beta}|$ was largest in the lateral lungs.

Conclusions: This is the first report of the three-dimensional breathing motion model parameters for a large cohort of patients. The model has the potential for noninvasively predicting lung motion. The majority of patients exhibited similar $|\vec{\alpha}|$ maps and the $|\vec{\beta}|$ maps showed greater interpatient variability. The motion parameter interpatient variability will inform our need for custom radiation therapy motion models. The utility of this model depends on the parameter stability over time, which is still under investigation. © 2009 American Association of Physicists in Medicine.
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I. INTRODUCTION

Accurate radiation therapy dose delivery to lung tumors often requires management of the tumor motion due to breathing. Motion management includes free breathing^{1–7} coupled with a method for modifying the dose delivery to account for motion, breath-hold,^{8–10} and breathing coaching,¹¹ where the patient uses biofeedback to guide their breathing pattern. Of these methods, free breathing allows the user to develop a process that minimizes involvement and cooperation of the patient beyond that typically required for radiation therapy treatments. This can be important for patients with limited cognitive function or patients with impaired breathing function.

Methods for modifying the dose delivery for free breathing patients include expanding the radiation portal to account for the motion,¹² gating the radiation delivery to synchronize the radiation delivery with the position of the tumor,^{13,14} and tracking the tumor motion with the radiation portal.^{15–17}

The free breathing treatment planning strategies involve the use of a breathing motion model to develop a patient-specific strategy. Often the model is based on CT scans ac-

quired during free breathing and organized using a simultaneously acquired breathing surrogate. The surrogate is typically a noninvasive measurement device such as a pneumatic belt placed around the abdomen, camera system that monitors a marker placed on the patient's abdomen or pelvis, or pressure sensor mounted to a belt that is wrapped around the abdomen.^{6,13} There are two surrogates used in our research group when we conduct CT scans for free breathing research: A pneumatic belt placed around the abdomen and a spirometer (Interface Associates, Aliso Viejo, CA, VMM 400). The spirometer has a measurement drift that does not allow its independent use, but coupled with the pneumatic belt signal, can provide a drift-free quantitative breathing metric, the patient's tidal volume, that can be compared against the reconstructed 4D CT scans.¹⁸

Verified breathing models have not yet been established. Many investigators have relied on the periodic nature of the breathing pattern to develop mathematical models in time using the assumption that the breathing motion can be accurately described as a function of time.¹⁹ Seppenwoolde *et al.*³ modeled breathing in this way using an even power of a

cosine function with adjustable period and amplitude. They found that this was able to fit the motion of embedded clips well, but also found that changes in breathing frequency or amplitude were difficult to model.

In some applications, explicit breathing models are assumed not to be required. For example, if a 4D CT scan is gated using phase angle-based gating, then each breathing phase is assumed to occur at a constant fraction of time during the breathing cycle. This allows the treatment planner to determine linear accelerator gating efficiency by identifying the fraction of the 360° breathing cycle for which the beam will be activated. However, the phase-based model assumes that breathing patterns are consistent and reproducible, an inaccurate assumption for many lung cancer patients.²⁰

Research^{21–28} on modeling the lung dynamic motion has been conducted with limited success. Most of the work, based on Weibel's model²⁹ on bronchial anatomy, has applied the principles of fluid dynamics or viscoelasticity to modeling lung motion. However, because of lack of detailed information on lung's inner structure, their results cannot be personalized. Their work can be used to understand the mechanical behavior of lung under different circumstances. The stress distribution without considering the airway resistance was established by Mead,³⁰ indicating that tidal volume may play an important role in modeling lung motion. Lambert *et al.*²³ established that there are pressure losses in the flow along the airway, from the periphery to the flow-limiting site. A linear relationship between the pressure loss and the flow rate was selected because of the low Reynolds's number found in the bronchial tree. In general, regions with stronger or weaker air resistance, corresponding to worse or better communications, longer or shorter airways from the trachea, will have lower or higher air pressure during inspiration, respectively. The opposite would therefore occur during exhalation, namely, that the regions that had lower pressure during inhalation would have greater pressure during exhalation.

Based on the relationship between pressure and airflow, and the fact that different regions of the lungs have different resistance to airflow, hysteresis, defined as differential tissue motion between inhalation and exhalation, has been hypothesized by Low *et al.*³¹ to be caused by pressure distribution imbalances during breathing and can therefore be related to airflow. For quiet respiration, a further model approximation is made here, namely, that the hysteresis motion is caused by the pressure imbalances and that the hysteresis motion magnitude is proportional to the airflow.

Finally, the motion model by Low *et al.*³¹ assumes that during quiet respiration, the motion component due to tidal volume changes is independent of the motion component due to pressure differentials and consequently airflow. Under this assumption, hysteresis motion due to pressure imbalances will occur with the same magnitude regardless of the tidal volume, and the tidal volume lung expansion component will not depend on the rate of breathing (at a single point in time).

The use of tidal volume and airflow to describe free breathing motion allows the time dependence of the model to exist outside the mathematical description of tissue motion.

FIG. 1. The breathing motion model (circles) of a piece of tissue determined from measured positions (crosses). $\vec{X}_0$, shown as a diamond, was the location of that tissue at the reference tidal volume and airflow, 0 l and 0 l/s, respectively. The displacement vector for a selected tidal volume and airflow is decomposed into the two components, $\vec{X}_v = \vec{\alpha}v$ and $\vec{X}_f = \vec{\beta}f$, which are the tidal volume and airflow components, respectively. The lines connecting the measured and fit locations are the discrepancies. The mean discrepancy in this case was 1.25 mm.

The time dependence lies in the behavior of the tidal volume and airflow and does not explicitly exist within the model equation. The positions of lung tissues are therefore hypothesized to be functions of five independent parameters; the 3D positions of the tissue at a reference tidal volume and airflow (typically 0 ml and 0 ml/s), the tidal volume, and the airflow.^{32,33}

As Low *et al.*³¹ hypothesized, the position of lung tissues can be described by a linear approximation in tidal volume and airflow. The original mathematical description has been modified here for clarity. The position of a piece of tissue lies at $\vec{X}_0$ at the reference volume and airflow. The position $\vec{X}$ at tidal volume v and airflow f is

$$\vec{X}(v, f; \vec{X}_0) = \vec{X}_0 + \vec{\alpha}(\vec{X}_0)v + \vec{\beta}(\vec{X}_0)f, \quad (1)$$

where $\vec{\alpha}(\vec{X}_0)$ and $\vec{\beta}(\vec{X}_0)$ relate the tissue position to the tidal volume and airflow, respectively, of the tissue at $\vec{X}_0$. Figure 1 shows an illustration of the breathing motion model superimposed with the data acquired from an enrolled patient.

This manuscript reports the breathing motion model parameters for lung cancer and nonlung cancer patients under quiet respiration. The parameters $\vec{\alpha}$ and $\vec{\beta}$ together provide a quantitative characterization of breathing motion that inherently includes the complex hysteresis interplay. The $\vec{\alpha}$ and $\vec{\beta}$ distributions were examined for each patient to determine overall general patterns and interpatient pattern variations.

II. METHODS AND MATERIALS

II.A. Data acquisition protocol

49 patients were enrolled under an IRB-approved protocol and scanned using a 16-slice CT scanner (Philips 16-slice Brilliance CT) operating in cine mode using 1.5-mm-thick

slices. Each contiguous set of the simultaneously acquired 16 CT slices was termed a couch position. The scanner was operated to acquire 25 scans per couch position using a 0.42 s rotation, 360° reconstruction, and 0.32 s between successive cine acquisitions, requiring 18.2 s to acquire the 25 scans. Eight or nine abutting couch positions were typically required to cover the whole lung. The in-plane field of view was 500 mm and images were reconstructed using 512×512 voxel matrices.

The tidal volume was acquired using a calibrated digital spirometer (Interface Associates, Aliso Viejo, CA, VMM 400) that was sampled at 100 Hz with 1 ml digitization resolution.^{34,35} The spirometer drifted, so a separate drift-free metric was acquired at the same time. An abdominal pneumatic belt (Philips Medical Systems, Cleveland, OH) was placed around the patient's abdomen and attached to a pressure transducer. The pressure decreased and increased during inhalation and exhalation, respectively, and the relationship between the bellows pressure transducer voltage signal and spirometry was found to be highly correlated over 18.2 s intervals when a linear drift correction was made to the spirometry signal.²⁰ The drift-corrected spirometry signal was used to recalibrate the bellows signal such that the final recorded values were tidal volume. To quantify the zero value of the tidal volume, the fifth percentile tidal volume was selected as 0 ml.

Because of sample-to-sample noise and digitization artifacts, the airflow was determined using a moving n th-order polynomial fit. n was selected to be 5 in this manuscript based on the observation that no significant improvement would be achieved by applying polynomial fit higher than fifth order. The airflow at time t was the analytical derivative of the fifth-order polynomial of the tidal volume measurement taken over a time span of 0.41 s (41 samples) centered at the point where the airflow was determined. This method of determining the derivative was selected because it reproduced the tidal volume signal with a marked reduction in the derivative noise, allowing for a relatively smooth determination of the airflow.

II.B. Image registration

In order to determine the motion model at each point, position measurements of each point of tissue in each CT scan dataset was required. In this study, a fast normalized cross-correlation (NCC) method was employed.³⁶ In order to determine the motion of a specific point of tissue, a small region with $11 \times 11 \times 10$ pixels that surrounded the point was identified and the NCC algorithm was used to locate that same region in the other 24 scans. One advantage of using the NCC model was that the determination of the maximum NCC was not sensitive to the variation in CT Hounsfield units found between inhalation and exhalation CT scans.

The CT scan with the tidal volume closest to 0 ml (exhalation) was selected as the reference scan for purposes of motion mapping. The CT scan length of 2.4 cm limited each multislice CT dataset to a small portion of the lung, typically 1/8. The magnitude of the motion at the inferior lung was

often greater than 3.0 cm. Some tissue regions, especially those close to the diaphragm, moved out of the longitudinal coverage of the dataset because the zero tidal volume scan was selected as the reference. This would give rise to two issues that could have compromised the results. First, the region being tracked would move out of the searching region but the NCC registration method would select a region within the couch position with largest correlation coefficient and produce spurious results. Second, if the region of interest moved out of the current couch position and was not tracked, some of the 25 scans would be unused.

In this study, the registration was performed in two directions, depending on the breathing phase relative to the reference phase. During exhalation, the tissue generally moved superiorly. Therefore, the multislice CT dataset was first categorized into two groups, inhalation and exhalation, respectively. Each group was sorted according to the tidal volumes from low to high. The reference scan was divided into a 3D mesh of abutting templates consisting of $11 \times 11 \times 10$ voxels, corresponding to $10.7 \times 10.7 \times 15$ mm³. The search region, cocentered with the template, had $21 \times 21 \times 20$ voxels, corresponding to $20.5 \times 20.5 \times 30$ mm³. The registration began with the scan that had the tidal volume closest to the reference scan tidal volume. Because 25 scans were acquired during respiration, there were enough tidal volume samples to limit the tidal volume change between two successive scans to less than 100 ml. The magnitude of motion corresponding to a tidal volume change of 100 ml was usually less than 8 mm. The search range used in this study had sufficient margins to allow for this much motion. When a matching tissue was identified, the displacements were recorded and accumulated to generate the new center of search region for the next scan. When the search region was expected to cross the boundary of the current couch position, the portion that moved out was replaced by the corresponding part of the scan in the next couch position with the closest tidal volume and its accompanying airflow as the reference template.

II.C. Model fitting

The registration process typically resulted in a set of 25 (x, y, z) locations for each evaluated point, along with the tidal volume and airflow corresponding to the acquisition time for each scan. The positions, tidal volumes, and airflows were fitted to the model, employing the Nelder–Mead optimization algorithm³⁷ by minimizing the root-mean least-squares average distance between the fitting and measurements,

$$\min_{\vec{X}_0, \vec{\alpha}, \vec{\beta} \in \mathfrak{R}^3} \sum_{i=1}^{25} \|\vec{X}_i - \vec{X}_0 - \vec{\alpha}v_i - \vec{\beta}f_i\|, \quad (2)$$

where $\vec{X}_i$ was the i th location of 25 measurements, and v_i and f_i were the tidal volume and airflow, respectively, for scan i . In Eq. (1), $\vec{X}_0$, $\vec{\alpha}$, and $\vec{\beta}$, vectors in $\mathfrak{R}^3$, were the overdetermined fitting parameters. Considering three independent components for each vector, nine parameters were determined by 75 measurements (25 sets of $\vec{X}_i$).

FIG. 2. The registration error of the normalized cross-correlation registration method employed in this study. The registration error is defined as the discrepancy between the displacement fields given by the registration method and manual tracking. 100 landmarks selected in the inferior part of lung from five patients were tracked and manually compared. The motion magnitudes of these landmarks varied from 10 to 30 mm.

One drawback with the Nelder–Mead method was that, like other multidimensional unconstrained optimization algorithms, it occasionally located a local minimum. To overcome this drawback and minimize the discrepancy of fitting, the fitting process was repeated at the current best point until the difference in discrepancies between two consecutive fitting operations fell below 5% of the discrepancy obtained from the previous fitting operation.

III. RESULTS

Figure 2 shows the registration error of the NCC registration method used in this study. Registration error was defined as the discrepancy between the displacement given by the registration and that given by manual tissue tracking. 100 landmarks were selected in the inferior portion of lung from five patients. The motion magnitudes of landmarks ranged from 10 to 30 mm. The mean registration error was 1.32 mm.

Figures 3 and 4 show the coronal and sagittal planar samples of $|\vec{\alpha}|$ and $|\vec{\beta}|$ in the left and right lungs of one patient with lung cancer. $|\vec{\alpha}|$, in units of mm/l, represents the

FIG. 4. Distribution of $|\vec{\beta}|$ in a normal pattern.

displacement of the tissue in the lung after inhaling 1 l. $|\vec{\beta}|$, with units of mm s/l, represents the tissue motion hysteresis at an airflow of 1 l/s. For this patient, the 85th percentile tidal volume was 665.0 ml and the airflow varied from -309.1 to 280.8 ml/s.

The result showed that $\vec{\alpha}$ was greater in the inferior and posterior portions of the lungs and smaller in the superior and anterior portions of the lungs. The craniocaudal component of $\vec{\alpha}$ dominated the displacement of the motion during the breathing cycle. $\vec{\beta}$ was greater in the lateral lungs. This pattern of $|\vec{\alpha}|$ and $|\vec{\beta}|$ distribution were observed in 44 out of 49 patients and was therefore defined as the normal pattern.

Figures 5 and 6 showed the coronal and sagittal projection of $|\vec{\alpha}|$ and $|\vec{\beta}|$ in the left and right lung of a patient that had an abnormal motion pattern. For this patient, the 85th percentile tidal volume was 460.1 ml and the airflow varied from -300.0 to 327.8 ml/s.

For this patient, in the right lung, $|\vec{\alpha}|$ was greater in the

FIG. 3. Distribution of $|\vec{\alpha}|$ in a normal pattern.

FIG. 5. Distribution of $|\vec{\alpha}|$ in an abnormal pattern.

FIG. 6. Distribution of $|\vec{\beta}|$ in an abnormal pattern.

inferior and posterior portions, while $|\vec{\beta}|$ was greater in the lateral lung. Both were similar to what was observed in the normal case. However, $|\vec{\alpha}|$ and $|\vec{\beta}|$ exhibited a different pattern in the left lung. Figure 5 shows that $|\vec{\alpha}|$ was greater in the superior and anterior portions of the left lung. Figure 6 shows that $|\vec{\beta}|$, instead of being greater in the lateral lung, was greater in the superior portion of the left lung, as indicated by arrows. The craniocaudal component of $\vec{\alpha}$ dominated the displacement of the motion during the breathing cycle. CT images reconstructed at a series of tidal volumes showed that the size of the left lung was only half of the size of the right lung, and the left diaphragm barely moved during inspiration. The dysfunction of left diaphragm caused the left lung breathing to be dominated by chest expansion, so the lung expanded in the anterior-posterior direction, which was well modeled by $\vec{\alpha}$.

Of the 49 patients, $|\vec{\alpha}|$ reached its maximum in the anterior lung in three patients, while for two other patients, $|\vec{\alpha}|$ was greatest in the lateral lung. For 45 out of 49 patients, $|\vec{\alpha}|$ reached its maximum in the inferior and posterior portions of the lungs. The hysteresis motion $\vec{\beta}$ had greater variability, but for the majority of patients, $|\vec{\beta}|$ was greatest in the lateral lungs.

The values of $|\vec{\alpha}|$ and $|\vec{\beta}|$ are three-dimensional scalar fields, so a histogram of the 85th percentile values was selected to describe the interpatient variability. Figure 7 shows the histogram of the 85th percentile of $|\vec{\alpha}|$ and $|\vec{\beta}|$ in all of the patients. The mean 85th percentiles of $|\vec{\alpha}|$ in the left and right lungs were 23.2 and 26.1 mm/l, respectively. The mean 85th percentiles of $|\vec{\beta}|$ in the left and right lungs were 3.7 and 3.6 mm s/l, respectively.

Figure 8(a) shows the cumulative histogram of discrepancies between the modeled and measured locations of all 49 patient datasets. The result indicated that for 80% of the lung tissues, the discrepancies were less than 1.75 mm, and for 90%, less than 2.14 mm. Figure 8(b) shows the cumulative histogram of relative discrepancies for motion magnitudes

FIG. 7. Histogram of the mean $|\vec{\alpha}|$ and $|\vec{\beta}|$ at the 85th percentile for 49 patients.

greater than 15 mm. The relative discrepancy was defined as the ratio of the discrepancy to the motion magnitude. For tissues where the overall motion was greater than 15 mm, 78% and 96% of the lung tissue positions had less than 10% and 15% relative position discrepancies, respectively. Figures 8(c) and 8(d) show the cumulative histograms of relative discrepancies for motions between 10 and 15 mm and motions between 5 and 10 mm.

IV. DISCUSSION

This is the first report of the three-dimensional breathing motion model parameters for a large cohort of patients. The overall $|\vec{\alpha}|$ and $|\vec{\beta}|$ maps varied smoothly as expected. $\vec{\alpha}$ and $\vec{\beta}$ described different breathing motion characteristics. $\vec{\alpha}$ modeled local lung expansion and could be interpreted as the breathing motion as if the patient breathed infinitely slowly. $\vec{\beta}$ modeled the hysteresis motion which was hypothesized to be caused by the dynamics of breathing. The relative magnitudes of $\vec{\alpha}$ and $\vec{\beta}$ are major determinates of the motion path eccentricity. In general, regions that had greater values of $|\vec{\beta}|$ corresponded to regions with greater $|\vec{\alpha}|$. These results showed that the majority of patients exhibited similar $|\vec{\alpha}|$ maps. The $|\vec{\beta}|$ maps showed greater interpatient variability with the common feature that $|\vec{\beta}|$ was greater in the lateral lungs.

The utility of the proposed breathing motion model is to noninvasively monitor and predict the motion of lung tissues and tumors using only external surrogates. The positions of any piece of lung tissue were hypothesized to be determined by the tidal volume and airflow. The implication of this hypothesis was that the position of a specific piece of tissue or tumor would be at the same location if given the same tidal volume and airflow, regardless of the point of time. It has been shown that the position of tumors varies at exhalation,³ in apparent contradiction to the model. The model, however, is based on tidal volume, which has a zero value at a selected percentile. This value is valid only for a day-to-day single scanning or treatment session. To compare the positions of tissues between sessions, an absolute lung volume surrogate would be required, for example, the total air content. Rather

FIG. 8. (a) Cumulative histogram of discrepancies between measured and fit locations. (b) Cumulative histogram of relative discrepancies to motion magnitudes over 15 mm. (c) Cumulative histogram of relative discrepancies to motion magnitudes between 10 and 15 mm. (d) Cumulative histogram of relative discrepancies to motion magnitudes between 5 and 10 mm.

than measure the total air content, the position of a piece of tissue, using an implanted surrogate for example, could be used to shift the tidal volume definition to correspond to the original 4D CT session.

Although airflow is the time derivative of tidal volume, the breathing motion model is an explicit function only of tidal volume and airflow. The tidal volume and airflow are themselves functions of real time. The assumption is made that a first-order relationship between the displacement and the surrogates will meet the clinical requirement in precision of dose delivery or treatment planning. For this study, 25 scans were acquired and good agreement between the measurements and the predictions from the breathing motion model was observed when the motion was greater than 15 mm, as illustrated in Fig. 8(b), with more than 90% of the points having less than 15% relative discrepancy. Since the average registration error in this study is 1.32 mm as illustrated in Fig. 2, the registered trajectory tends to be more relatively dispersive in less active points, when the registration error gains more weight in the motion magnitude. Therefore, it is not surprising that the model performs worse for points that move less, as illustrated in Figs. 8(c) and 8(d). However, 90% of the points still exhibited better than 2 mm agreement.

In this study, 25 scans were acquired for each couch position, while the breathing motion model had only nine independent parameters. Theoretically, three scans acquired at different tidal volumes and airflows would have provided sufficient motion data to fit the model parameters. Errors in registration and motion-induced image artifacts would still cause errors in motion parameter determinations. The use of additional CT scans was expected to reduce the impact of

individual registration errors, but at the cost of dose to the patient. The minimum number of scans and optimization of the breathing phases of those scans remains an open question.

The ultimate utility of the motion model will be a function of its stability. If the breathing motion model parameters change significantly between sessions (either imaging or treatment), the specific motion model would be useful only for single-session activities, such as removing motion artifacts from nuclear medicine images. If the motion model parameters are stable for weeks exclusive of disease progression or treatment response, it would be useful for supporting radiation therapy treatment planning, including optimization of linear accelerator gating windows. If the model was stable over timescales consistent with the course of radiation therapy for unirradiated and healthy lungs, changes in the model might be used to monitor disease progression or radiation response. We are currently conducting scans in series to determine the model stability.

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